Clinical and Epidemiological Observations Regarding the 1998 Kauai Murine Typhus Outbreak

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Abstract

Five cases of murine typhus occurring on southwestern Kauai in 1998 are described, following an investigation by the Department of Health. Two cases also had concurrent leptospirosis. Recent habitat changes of peridomestic animals and their fleas may have increased the risk for developing murine typhus. Increased suspicion of typhus by island physicians and more aggressive rodent control activities are recommended.

Introduction

Murine typhus was first diagnosed in Hawaii in 1933 and reported by Fennel in 1934.[1] The diagnosis was based on clinical findings, positive Weil-Felix reactions, and protection tests carried out by the U.S. Public Health Service in guinea pigs with serum from suspected cases. The earliest clinical and epidemiological features of the disease in humans were published in 1938 and 1941.[2, 3] The incidence of typhus in Hawaii peaked in fiscal year 1944 when 186 cases were reported; Oahu accounted for 149 (80%) cases, Maui for 28 (15%), Kauai for 7 (4%), and Hawaii for 2 (1%) cases. The low prevalence on Kauai and Hawaii was the result of higher rainfall than was observed on Oahu and Maui, which is not ideal for typhus.[4] Cases were controlled at the end of World War II by dusting Dichloro-Diphenyl-Trichloroethane (DDT) into rodent burrows. By 1950, only 12 cases were reported in the Territory of Hawaii. During this time, national reported annual incidence of murine typhus dropped from more than 5,000 cases in the 1940s to fewer than 100 in the 1980's.[5]

The Kihei area of Maui became recognized as a hyperendemic area for murine typhus in 1972, and accounted for most of the recently reported cases in the State of Hawaii.[6] From 1994 through 1998, 33 cases were reported to the State of Hawaii Department of Health (DOH): 24 from Maui, three from Molokai, one from Oahu, and five from Kauai.

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The five cases of murine typhus from Kauai occurred on the southwest coast of the island in 1998. This occurrence is unusual because Kauai had never been recognized as having an endemic focus of murine typhus. The last previously reported case from the island was in 1982. These five cases represent the highest annual incidence of the disease on Kauai since the 1940s. This paper reviews the clinical and epidemiological features of the 1998 murine typhus outbreak on Kauai, and offers a hypothesis as to why the southwest region of Kauai may be emerging as a new endemic site for murine typhus in the State.

Methods

The DOH was notified of five positive serologic test results for murine typhus on Kauai during 1998. A laboratory confirmed case was defined as a person with a clinically compatible illness having a four-fold rise in IgG antibody titer to typhus group antigen as detected by the Indirect Fluorescent Antibody (IFA) test with a minimum convalescent titer of 1:64 in specimens taken $\geq$ two weeks apart. A probable case was defined as a patient with a single IgM or IgG IFA titer to typhus group antigen of $\geq$ 1:128.

Each person with a positive serologic test was interviewed by the Kauai epidemiological specialist, and a standard epidemiology Case Investigation Report form was completed. Clinical and epidemiologic information was abstracted from outpatient and hospital medical records. Age, sex, residence, rodent and flea exposure, date of illness onset, duration of illness, symptoms and signs, laboratory test results, course of illness, therapy, and outcome for each person was reviewed. Five acute murine typhus infections were documented.

The DOH Vector Control Branch performed rodent trapping at the homes of three of the five cases. Rats were trapped, sprayed with a synthetic pyrethroid aerosol in the field to reduce fleas, and transported to the Kauai Vector Control Laboratory for processing. No flea isolation or identification was performed. The rats were euthanized, and tissues and organs were examined and processed. Rat serum samples for IFA tests against *Rickettsia typhi* were obtained by heart puncture. Rodent tissue and serum samples were then sent to the Vector Control Branch Laboratory in Honolulu where the serologic tests were performed. Statewide rodent testing between 1992 and 1998 included IFA testing for *R. typhi,* and rodent kidney cultures for leptospirosis.

Results

Two of the cases were confirmed, and three were probable. The

cases occurred throughout the year along the southwest coast of Kauai. There was no seasonal trend. The first case occurred in Kekaha during April. The second case occurred in August at Makaweli. Two cases occurred in the same neighborhood in Waimea during October and November. The fifth case occurred in Kekaha at the end of December.

Four of five cases had rodent and flea exposure around their homes. The fifth case had a pet kitten infested with fleas. Rats trapped at the homes of the cases in Makaweli and Waimea were positive for *R. typhi* by IFA serology.

The cases ranged from 33 to 80 years of age with a median age of 42 years. The male/female ratio was 4:1. Signs and symptoms during the course of illness are summarized in Table 1. The mean duration of illness was 11 days with a range of five to 17 days. One patient was treated as an outpatient for mild illness that was characterized by fevers, sore throat, gastrointestinal symptoms, myalgias, headache, photophobia, and cough. He had the longest duration of illness with a remitting and relapsing course and a prolonged period of convalescence.

Table 1.— Clinical Manifestations During the Course of Murine Typhus

Manifestation	Number
Fever	5/5
Headache	4/5
Myalgias	4/5
Elevated Liver Enzymes	4/4
Chills	3/5
Hypotension	3/5
Cough	3/5
Pneumonitis	2/5
Macular Rash	2/5
Conjunctivitis/Conjunctival Suffusion	2/5
Pharyngitis	2/5
Arthralgias	2/5
Night Sweats	2/5
Abdominal Pain	2/5
Vomiting	1/5
Diarrhea	1/5
Increased Urinary Frequency	1/5
Thrombocytopenia	1/5
Microscopic Hematuria/Pyuria	1/5
Cervical Lymphadenitis	1/5

Four cases required hospitalization. The mean duration of hospitalization was 5.5 days with a range from four to seven days. The hospitalized patients all presented with an acute undifferentiated febrile illness, headaches, chills, and myalgias. Three cases had severe hypotension requiring fluid resuscitation. Two patients were admitted with a macular erythematous skin eruption located on the face, chest, back, abdomen, and proximal upper extremities. Two had pneumonitis on chest x-ray. All four hospitalized cases had hepatic serum enzyme abnormalities consistent with hepatitis. Lactate dehydrogenase was increased in two patients with peak values of 2,382 U/L, and 1,247 U/L. All four cases had moderate peak elevations of aspartate aminotransferase (AST, SGOT) with a range 92 U/L to 687 U/L, and alanine aminotransferase (ALT, SGPT) with a range 300 U/L to 698 U/L. Alkaline phosphatase was moderately elevated in three cases. Clinical jaundice did not occur, and bilirubin levels were normal. Blood cultures were negative.

Thrombocytopenia occurred in one case. The peripheral white blood cell count was normal in all cases, but two cases had increases in the percentage of bands in the differential count. Hemoglobin was minimally reduced in two cases. Renal function was normal. Urinalysis was abnormal in only one case demonstrating both microscopic hematuria and microscopic pyuria.

The Weil-Felix screening test was performed in three cases. A positive Weil-Felix reaction titer is ≥1:160. All three were OX-19 positive. Two cases also were OX-K positive. One case was positive for OX-19, OX-K, and OX-2 antigens. Two patients had acute IgM antibody titers by IFA of 1:64 to typhus group antigens. All had convalescent IgG antibody titers by IFA ≥ 1:256 to typhus group antigens. Two cases had serologic evidence of concurrent leptospirosis infection by demonstrating positive acute and convalescent microscopic agglutination test titers for *Leptospira interrogans* serogroup Australis.

Table 2 lists the initial diagnoses, serologic diagnoses, treatments, and outcomes of these five cases. The nonspecific nature of the illness made clinical diagnosis difficult. These cases presented with initial diagnoses of Rocky Mountain spotted fever (RMSF), viral syndrome, urosepsis, sepsis, and pneumonia. The attending physicians considered leptospirosis and rickettsial disease in the differential diagnosis of all five cases.

Table 2.— Initial Diagnosis, Serology, Treatment (Rx), And Outcome For The Five Murine Typhus Cases

Initial Diagnosis	Typhus Serology†	Leptospirosis Serology‡	Rx	Outcome
Rocky Mountain Spotted Fever	≥ 1:256	Negative	D/Di	Recovery
Viral Syndrome	≥ 1:256	Negative	D	Recovery
Urosepsis	≥ 1:256	Negative	D/C	Recovery
Sepsis	≥ 1:256	1:800	D/C	Recovery
Pneumonia	≥ 1:256	1:400	T/C	Recovery

†IgG indirect immunofluorescent antibody assay against typhus-group antigen

‡Microscopic agglutination test for *Leptospira interrogans* serogroup Australis

D = Doxycycline, C = Ceftriaxone, T = Trovofloxacin, Di = Dicloxacillin

Appropriate antibiotic therapy was promptly initiated in all the cases. Clinical improvement occurred quickly following antibiotic administration and fluid resuscitation. Most patients became afebrile two to four days after the start of antirickettsial therapy. Four patients received a therapeutic course of doxycycline, and one patient completed a course of therapy with trovofloxacin. All received a beta-lactam antibiotic during the period of therapy to treat presumptively for other bacterial infections pending blood and body fluid culture results. All patients recovered without complications.

Tables 3a and 3b summarize statewide rodent testing data between 1992 and 1998. Testing was done on rodents trapped during community surveys throughout the state, as well as at probable exposure sites when cases of murine typhus and leptospirosis were reported. The high rodent typhus prevalence on Maui was the result

of trapping focused in the hyperendemic area of Kihei. Until the outbreak on Kauai was reported, rodent trapping was focused on the east side (wetter area) of the island where leptospirosis cases were more prevalent. In spite of the low overall typhus prevalence on Kauai, 1998 trapping conducted around exposure sites of the cases from Makaweli and Waimea showed that four of eight rats trapped were positive for typhus. Rodent trapping was not conducted in Kekaha. Statewide infection rates for leptospirosis in humans and rodents have historically been highest on the islands of Hawaii and Kauai in areas of high rainfall. The rodents trapped in Makaweli and Waimea were not cultured for leptospirosis.

Table 3a.— Rodent Testing In Hawaii: 1992-1998[1]
Murine Typhus

Island	Murine Typhus		
	# Tested	# Pos	% Pos.
Hawaii	3948	16[a]	0.4
Maui	1308	213[b]	16.3
Oahu	1629	32[c]	2.0
Kauai	1590	20[d]	1.3

Table 3b.— Rodent Testing in Hawaii: 1992-1998[1]
Leptospirosis[2]

Island	Leptospirosis		
	# Tested	# Pos	% Pos.
Hawaii	7651	1840	24.0
Maui	205	0	0
Oahu	2692	314	11.7
Kauai	2158	237	11.0

[1] Number of animals tested varied by disease because mongooses and mice were not tested for typhus, and because of periodic personnel shortages. There are no mongooses on Kauai.
[2] Leptospirosis testing included mongooses, rats and mice. On Maui, rodents trapped during the Kahului residential surveys were not tested for leptospirosis, nor were animals captured during routine surveillance.

[a] Typhus-positive rodents were recovered from Honolii, Papaikou, Panaewa, Kealia, Kukuihaele, Kalaoa, Waikoloa, Kukaiau, and Kailua-Kona.
[b] Typhus-positive rodents were recovered from Kula, Wailuku, Waihee, Haiku, Paia, Kahului and Kihei (majority).
[c] Typhus-positive rodents were recovered from Nanakuli and Waialua.
[d] Typhus-positive rodents recovered from Hanamaulu, Kaumakani, Koloa, Waimea, Lihue, and Makaweli.

Discussion

Epidemiology

Murine typhus is a zoonotic disease caused by *Rickettsia typhi*. Commensal rats of the genus *Rattus* are the primary reservoirs of *R. typhi*. The oriental rat flea, *Xenopsylla cheopis* (Rothschild), is the principal vector, but the cat flea, *Ctenocephalides felis* (Bouche), has also been found to be naturally infected with *R. typhi*. *C. felis* was found by Azad [7] to be at least equal to *X. cheopis* for the propagation of the rickettsial organism. *C. felis* readily feeds on humans and many alternative hosts, and is generally more abundant in endemic foci. *R. typhi* infects its host through the inoculation of infected flea feces into abraded skin or through mucous membranes. Inhalation of dust containing infectious flea feces may also be responsible for disease transmission.[8]

Since 1972, the number of cases of murine typhus in Hawaii has increased, especially on Maui.[6] The macroenvironment of murine typhus consists of a hot, dry climate with little rainfall. The murine typhus microenvironment includes the intimate life cycle of rodents and their fleas, and an adequate food supply for the rodents. Fleas do not propagate as successfully in wet environments where the soil is damp as they do in dry environments, so few cases of murine typhus occur in areas of heavy rainfall. Ecologic conditions in Hawaii have changed considerably since the end of World War II. Conditions currently influencing rodent-flea cycles have become less dependent on unsanitary housing and overcrowding, and are more dependent on macroenvironment and microenvironment conditions. The most notable ecologic changes included: 1) modern sanitary housing codes requiring rat-proof structures; 2) the encroachment of suburbia on agricultural land; 3) changing agricultural practices such as conversion of farrow to drip irrigation and converstion of sugar cane land to seed corn or other crops; and 4) subtle climatic changes (El niño and global warming) influencing rodent nesting micro-temperature and humidity that favor specific rodent and flea species. A recent article by Chan[9] describes a model for the assessment of climate change and infectious diseases that may be useful for future research related to the ecology of murine typhus in Hawaii.

Disease transmission correlates with specific flea species and flea population size rather than the population of rodents. Certain flea species, especially *X. cheopis* or *C. felis*, are more critical than others for the maintenance of the characteristic rat-flea-rat cycle that enables the transmission of *R. typhi*. Eradication of fleas from a typhus-carrying rodent population theoretically would eliminate the disease in a community.

As a result of the earlier anti-typhus campaign conducted in Hawaii during the late 1940s and early 1950s, the population of the Norway rat, *Rattus norvegicus*, and the oriental rat flea, *X. cheopis*, near human dwellings has dramatically declined. The reduction of both reservoir and vector has been primarily attributed to the implementation of rat-proofing methodologies in new homes and buildings and the emphasis on eliminating rodent harborages in the domestic environment. Most of the earlier literature on murine typhus indicated that the primary reservoir and primary vector was *R. norvegicus* and *X. cheopis*, respectively.[4,7,10,11] Why have the number of cases of typhus increased in the absence of significant numbers of the primary reservoir and vector in and around homes in Hawaii since 1972?

Mohr[4] discussed the similarities between the ecology of murine typhus and murine plague emphasizing the importance of the flea breeding cycle in the perpetuation of both diseases. Classical urban plague involving domestic rodents and the oriental rat flea was self-limiting because the bacteria killed the reservoir and vector, and the disease disappeared within a few years. Sylvatic plague is a zoonoses

perpetuated among true reservoir animals (e.g. groundhogs, marmots, prairie dogs) and their respective flea species. The plague bacillus does not kill its reservoir host, and fleas continue to transmit the organism from host to host. Hawaii did not have a natural sylvatic plague host. However, the plague bacillus in Hawaii persisted for more than 40 years in sugar cane fields in the Hamakua region of Hawaii, and the Makawao region of Maui in the Polynesian rat, *Rattus exulans* (Peale), and the Hawaiian rat flea, *Xenopsylla vexabilis* (Jordan).[13,14] The microenvironments of the ground burrows of the Polynesian rats in the sugar cane fields were ideal for flea breeding.[15] The few human cases of plague that occurred following the urban epidemics probably resulted from accidental exposure to infected rodent burrows in sugar cane fields or from Norway rats or domestic animals (dogs or cats) transporting infected fleas from sugar cane field burrows to adjacent homes. It is postulated that a similar rat-flea-rat cycle for murine typhus may be present in some sugar cane fields or other agricultural setting providing a protected microenvironment for nesting rodents.

Recent studies of murine typhus in California suggest that the classic rat-flea-rat cycle of *R. typhi* have been replaced by a peridomestic animal cycle involving feral cats, dogs, opossums and their fleas. A second typhus group rickettsia, *R. felis*, has been discovered in cat fleas and opossums in southern California and Texas.[16,17] The inappropriate feeding and lack of control of the feral cat population in a community with the unintended increase of both the cat and rodent populations could result in murine typhus outbreaks.

The three West Kauai homes examined by the Vector Control Branch maintained some features of an agrarian lifestyle. Domestic animal food and shelter outside domestic residences attract and support populations of commensal rodents. It is not surprising that typhus-infected *R. rattus* and *R. norvegicus* species were trapped on these properties.

Dust in certain protected rodent harborage areas may contain infectious flea feces for years even after the rodents have been eradicated from the area. This may partially explain why murine typhus cases on Maui and Kauai occur throughout the year. In addition, seed corn has replaced sugar cane as an island crop in many locales on Kauai. Seed corn is a better nutrient source for rodents than is sugar cane. A better food source can sustain a larger rodent population and is postulated to enhance rodent migration to human dwellings when crops are harvested. These occurrences may have collectively increased rodent-flea populations, peridomestic animal-flea populations, and vector-borne disease in the area. Further research is needed to determine if the murine typhus cases on Kauai reflect changing community-wide ecologic conditions on the southwestern coast before it can be concluded that the region has become a hyperendemic area for murine typhus.

Clinical Description

Murine typhus is an acute illness characterized by fever, chills, headache, and myalgias. A diffuse macular or maculopapular rash occurs in 50% of cases, and is usually located on the trunk, arms, legs, and face. If the rash occurs, it is present at the time of the initial physician examination in 18 % of cases. The rash appears six days (range 0 to 18 days) after the onset of fever. Petechiae are noted in $\leq$ 10% of cases.[5] Respiratory tract symptoms including sore throat and cough can occur, and chest x-ray can reveal pulmonary infiltrates consistent with a pneumonitis. Gastrointestinal symptoms are common and include abdominal pain, anorexia, nausea, vomiting, and diarrhea.[5] Physical examination may reveal hepatomegaly (25% of cases) or splenomegaly (10% of cases).[5,19] Jaundice is uncommon but has been reported in 11% of cases in one series.[20]

Serum aminotransferase levels are elevated three to five times baseline in 90% of cases, and > five-fold in about 25% of patients.[5,20] The peripheral white blood cell count is usually normal, but mild leukocytosis and leukopenia have been reported. Anemia can occur. Mild thrombocytopenia is common, and occurred in 46% of cases in one review. Hypoalbuminemia (89%), hypocalcemia (79%), hyponatremia (60%), and hypoproteinemia (45%) are common serum chemistry abnormalities that reflect the widespread vascular endothelial cell injury from *R. typhi* infection.[5,21]

Most patients with murine typhus require hospitalization. Three of the cases in this review had hypotension requiring fluid resuscitation, and presented with syndromes of shock, sepsis, pneumonitis, unexplained febrile illness, and anicteric hepatitis. The reported complications of murine typhus include renal failure, meningoencephalitis, myocarditis, endocarditis, respiratory failure, hepatic insufficiency, hematemesis, and severe hemolysis when associated with glucose-6 phosphate deficiency or other hemoglobinopathy. Death occurs in 1% to 4% of patients.[5,19-24]

Diagnosis

The Weil-Felix agglutination reaction is non-specific, insensitive, and no longer recommended as a screening or diagnostic test for murine typhus. The diagnostic test of choice for *R. typhi* is the IFA to typhus group antigens. Confirmation of the diagnosis is seen with a fourfold antibody titer rise between acute and convalescent serum samples to a titer of $\geq$ 1:64. A probable diagnosis can be made within the first week of illness with if single IgM or IgG titer is $\geq$ 1:128. The IFA test cannot differentiate between *R. typhi* and *R. felis*. Polymerase chain reaction testing is necessary to differentiate these two organisms, but this test is available at only a few research centers.[19,21]

The diagnosis of murine typhus relies upon a high degree of clinical suspicion and the collection of acute and convalescent serology for specific antibody testing. Physicians in Hawaii should consider murine typhus in the differential diagnosis of acute undifferentiated febrile illness, viral exanthem, sepsis, unexplained acute multi-system illness, leptospirosis, acute hepatitis, pneumonitis, and aseptic meningoencephalitis. A history of exposure to rodents or fleas is not always present. The occurrence of fever and rash is suggestive, but the rash is nonspecific and not always present. RMSF can be confused with murine typhus, but RMSF is not endemic to Hawaii. Human ehrlichiosis has a similar clinical presentation, but leukopenia and thrombocytopenia is more significant. Human ehrlichiosis is not endemic to Hawaii. RMSF and ehrlichiosis should be considered in travelers recently returning from endemic areas for those diseases. A concurrent diagnosis of leptospirosis was established in two (40%) of our patients.

Rodents are reservoirs for leptospirosis. Serologic testing for leptospirosis should also be performed whenever the diagnosis of murine typhus is considered.

Treatment

The treatment of choice for murine typhus is doxycycline 100 mg twice a day orally or intravenously continued until 48 hours after fever resolves or for a minimum of five days. Chloramphenicol is the drug of choice in pregnant women, and is prescribed at a dose of 50 mg/kg/day in four divided doses intravenously for the same duration.[19,21] Oral chloramphenicol is not available at the present time in the United States.[21] Relapses have been reported with chloramphenicol. There have also been reports of successful treatment of murine typhus with various quinolone antibiotics such as ciprofloxacin.[25] Because murine typhus can be severe or even fatal, appropriate specific therapy should begin promptly without waiting for serologic confirmation if clinical and epidemiologic clues raise suspicion for this diagnosis. Appropriate antibiotic therapy results in prompt clinical improvement and shortens the duration of fever.[8]

Doxycycline is also effective for mild to moderate cases of leptospirosis. More severe cases of leptospirosis are treated with intravenous penicillin G, ceftriaxone or ampillicin.[26]

Prevention

Prevention is directed toward rodent and flea eradication programs. The DOH must be notified of all murine typhus cases as soon as possible in order to monitor the rodent/flea population and take appropriate action to prevent further disease spread. The DOH Vector Control staff is available for rodent trapping, and flea eradication at exposure sites. People cleaning enclosed areas that may harbor rodents should wear a protective mask or respirator to avoid inhalation of dust containing flea feces. Skin should be protected from flea feces by covering exposed areas with appropriate clothing such as long sleeved shirts, long pants, socks, and shoes, and use of topical insect repellents.

Conclusion

The five cases of murine typhus in southwest Kauai in 1998 are probably the beginning of a new hyperendemic focus of typhus in Hawaii. The changing environmental conditions in this region may result in additional cases in the future. Monitoring of reservoirs and vectors in this region is required in order to determine the timely application of control measures to prevent human disease. Local physicians should be cognizant of the widespread murine typhus reservoirs and vectors in the State, and maintain a high degree of suspicion for the diagnosis of murine typhus in acute undifferentiated febrile illnesses especially with unexplained liver enzyme elevations.

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